

*Jaundice in Hodgkin's Disease*

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Jaundice is not rare in Hodgkin's disease. The average incidence according to the literature ranges from 3 to 8 per cent.<sup>1-6</sup> When patients with widespread Hodgkin's disease develop jaundice, and after the obvious causes of jaundice, such as transfusion reactions, are ruled out, most clinicians ascribe the icterus to obstruction by compression or obliteration of the extrahepatic biliary ducts by Hodgkin's tissue. We undertook this study to confirm or deny this prevailing concept of jaundice in Hodgkin's disease.

Although the role of obstruction is generally conceded to be the important one, several other jaundice-producing diseases which may be associated with Hodgkin's disease must be considered as well as all coincidental entities that produce jaundice. The former group includes viral hepatitis, important because of the increased exposure to this disease which patients with Hodgkin's disease undergo when they receive large quantities of transfused blood or are intentionally inoculated with the virus of hepatitis as a therapeutic procedure as suggested and carried out by Hoster<sup>7</sup> (1949) after he had observed long remissions in patients with Hodgkin's disease who contracted viral hepatitis.

The second associated entity is that of hemolytic anemia. Aside from the normally occurring hemolysis of transfused blood (20 per cent), and that occurring in transfusion reactions, a distinct complicating hemolytic anemia syndrome has been described in Hodgkin's disease by Dameshek and others.<sup>8-9</sup> This has been classified by some as secondary hypersplenism. The spleen in these cases is generally involved by Hodgkin's disease. The mechanism of increased blood destruction is obscure. However, increased osmotic fragility is the rule and

spherocytosis may be demonstrated.

The above modalities have been dismissed because: 1) No evidence of acute viral hepatitis was found in our studied material; and 2) clinical evidence supporting any hemolytic pathogenesis of jaundice in our cases was absent.

Our main consideration, therefore, will be jaundice produced by the obstructive mechanisms of Hodgkin's disease. Coronini, cited by Wallhauser<sup>2</sup> in 1928, outlined the following mechanisms of jaundice in Hodgkin's disease, all of which are obstructive in nature:

1. Obliteration of the common duct alone.
2. Compression of the common duct alone.
3. Changes in both the extra- and intrahepatic ducts.
4. Changes limited to the intrahepatic ducts.

Opinion concerning the site of obstruction is divided; the current consensus would seem to favor the extrahepatic mechanisms. Symmers,<sup>1</sup> although favoring the extrahepatic genesis, describes jaundice in cases showing only intrahepatic duct obstruction by the lesions of Hodgkin's disease. It was Barron<sup>3</sup> in 1926 who stated, "It is likely that peribiliary infiltration produces jaundice more frequently than does pressure by enlarged lymph nodes or tumor masses against the large bile ducts." This variation on the emphasis has served as an additional stimulus for this study in the hope of adding some weight to one or the other side. The terminology used by us is that outlined by Jackson and Parker,<sup>10</sup> viz, Hodgkin's paraganuloma (no cases), Hodgkin's granuloma and Hodgkin's sarcoma.

For this study we selected forty cases of Hodgkin's disease coming to autopsy at the Memorial Center for Cancer and Allied Diseases within the past five years. Twenty-

three of the forty patients were jaundiced at death and sixteen of these had Hodgkin's granuloma with liver involvement; three had Hodgkin's sarcoma with liver involvement by Hodgkin's disease. Sixteen cases serving as controls were not jaundiced, but had Hodgkin's disease in their livers. In one non-icteric Hodgkin's case there was no involvement with hepatic Hodgkin's disease but massive hepatic amyloidosis which will be discussed later.

On examining the gross autopsy protocols in our jaundice cases, which include the latter two types of Hodgkin's disease, in only two was the jaundice considered to be due to extrahepatic obstruction. There was obstruction by paracholodochal lymph nodes in one instance and obstruction at the porta hepatis in the other. However, in none of our cases presenting jaundice was there microscopic evidence of extrahepatic obstruction such as intrahepatic duct dilatation, biliary cirrhosis or both. Bile thrombi were present in the terminal canaliculi in our most severely jaundiced cases, however. Lacking evidence to support the extrahepatic obstructive theory we attempted to find a common denominator in the livers of the jaundiced patients having liver involvement as compared with liver involvement by Hodgkin's disease in patients without jaundice.

The granuloma group will be discussed first.

In this group the males were predominantly affected with regard to the liver; this observation is consistent with the sex incidence of Hodgkin's granuloma as a whole, 1.9/1. What is more interesting is the male dominance in the jaundiced patients with Hodgkin's granuloma, 4.3/1.

Our microscopic findings in Hodgkin's granuloma involving the liver, with and without jaundice, are as follows:

In all sixteen cases of jaundice, practically all of the portal triads were involved by Hodgkin's granuloma and fibrosis of the Hodgkin's tissue was marked. The degree of fibrosis of Hodgkin's tissue in other organs as compared with the liver has not been assessed. The size of the nodules per se apparently played no significant part in the production of jaundice. In thirteen cases

in which there was no jaundice, there occurred either one of these changes, i.e., fibrosis or the diffuse periportal localization of Hodgkin's disease—but not both. In cases showing marked fibrosis, many portal trinites were uninvolved by Hodgkin's disease. In those showing diffuse periportal involvement, fibrosis was absent or minimal.

The above observations do not apply to the cases of Hodgkin's sarcoma. In the six cases of Hodgkin's sarcoma, the sex incidence is 1:1. The small number of the cases studied precludes anything but a superficial and speculative conclusion regarding the etiology of jaundice in the group. One difference was noted, however. In the three non-jaundiced patients with Hodgkin's sarcoma, the intervening liver tissue was relatively intact, while in the three jaundiced ones, the liver tissue was necrotic. The etiology of the necrosis is obscure, but hepatotoxic drugs and disturbances in liver circulation must be considered.

Of the remaining five miscellaneous cases, the instance of hepatic amyloidosis is included because of jaundice in the patient which occurred several months before death but subsequently cleared. Although massive diffuse hepatic amyloidosis may produce jaundice, it is rare, and the etiology of the earlier jaundice in this case cannot be determined.

Of the remaining four miscellaneous cases in which there was jaundice without liver involvement by Hodgkin's disease, the patient with posthepatic cirrhosis had been non-icteric until four months before death when he developed a classic case of viral hepatitis. He remained jaundiced until death.

The finding of massive centrilobular congestion and necrosis in one case suggested distal venous obstruction, although this feature could not be demonstrated at autopsy.

In two cases there was no gross or microscopic evidence of liver disease although there had been mild jaundice which appeared twenty-four hours prior to death in the one case and forty-eight hours before death in the other. No anatomic cause, including unrelated exogenous causes, could be found.

From our study we would like to submit the following conclusions:

1. Obstruction of the extrahepatic biliary ducts played no demonstrable part in the production of jaundice in the cases studied and, on this basis, it would appear to be, at most, an infrequent cause.

2. Patients with jaundice showing liver involvement by Hodgkin's granuloma, demonstrated diffuse involvement of the portal trinites with fibrotic Hodgkin's disease.

3. Non-jaundiced patients with liver involvement by Hodgkin's granuloma did not show this complex.

4. In patients with liver involvement with Hodgkin's sarcoma the etiology of jaundice is not clear, but intervening liver necrosis in the cases with jaundice was demonstrated, while it was absent in the non-jaundiced patients.

5. Patients developing jaundice immediately prior to death may show no histologic evidence of liver disease.

It is certain that there are exceptions to this over-all thesis. Borderline qualitative and quantitative changes with regard to considering a case as one of jaundice from the study of the liver sections alone will be seen, and in any given case multiple causal factors may be operative, or no cause found. This study is presented to stimulate re-evaluation of the older concepts regarding the genesis of jaundice in Hodgkin's disease.

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#### DISCUSSION

ALFRED ANGRIST: I have encountered several cases of jaundice with extrahepatic occlusion by Hodgkin's disease, and I wonder whether others have not had the same experience.

DOUGLAS SUNDERLAND (by invitation): I should like to ask Dr. Beatty if, in his jaundiced patients with Hodgkin's granuloma with marked fibrosis, he found any correlation with ascites.

ARTHUR C. ALLEN: In those cases you just referred to, Dr. Angrist, of extrahepatic obstruction by nodes, I wonder if there was intrahepatic involvement causing the jaundice.

ALFRED ANGRIST: Yes, but the impression was that the jaundice was caused by stenosis of the larger ducts. I know this does occur, and I wonder what Dr. Beatty's experience has been. One of the explanations offered, at least by myself, in explaining the failure of dilatation to occur proximal to the obstructive lesion in the duct, has been that the fibrosis has extended along the duct structures and that this has prevented the dilatation. The jaundice that appears in these cases does not last as long clinically as is the common story of obstructive jaundice as it occurs in carcinoma of the head of the pancreas. At least it has been my experience that the jaundice in Hodgkin's disease is a pretty lethal symptom. I wonder what the duration and extent of the jaundice was in the group of cases presented. In cases where the extrahepatic or larger intrahepatic ducts are involved, it is a progressive, inevitable, continuing jaundice of the Courvoisier's type, and I wonder whether that was the finding in this series of cases.

THOMAS G. MORRIONE: I wonder whether Dr. Beatty did reticulum stains on these livers. The reason I ask is that I believe that one is better able to judge the degree of fibrosis by the reticulum stain, especially if one combines it with the trichrome stain. One may arbitrarily define the degree of fibrosis as that which is detectable or visible with the H and E stain, but in

the past we found this method unsatisfactory. In attempting to correlate the histologic grading (zero to four plus) of fibrosis in cirrhotic livers with quantitative chemical collagen data, the two sets of data did not coincide well at all. Even trichrome-stained preparations did not enable us to accurately predict the collagen content. It was only when we used the reticulum stain that we were able to obtain very good correlation between our grading of the degree of fibrosis (accepting reticulum as collagen, as most people will) and the chemical data. I do not mean to imply that Dr. Beatty's conclusions would necessarily be different, but I would feel a little more satisfied about the accuracy of the grading of the fibrosis.

**EDITH E. SPROUL:** Dr. Beatty mentioned very briefly that he thought some of the therapeutic agents he mentioned in Hodgkin's disease might have been injurious to the liver. I wonder if he will speak about that.

**ALFRED ANGRIST:** If the summation of such focal intrahepatic involvement in the biliary triads is effective on an obstructive basis, why don't we see more often bile casts in the terminal canaliculi? It has been my impression that they do not occur very often in relation to intrahepatic Hodgkin's, although I have not made a directed survey of this.

There are still other mechanisms of jaundice that can apply. It is not at all uncommon, and I imagine you eliminated this type of case from your group, to see a patient with Hodgkin's disease, like lymphosarcoma, develop a rapid anemia, undoubtedly on the basis of hemolysis, which can contribute to overburdening a liver, not too well because of the severe illness of the patient, and thus contribute to the jaundice, so that some of the jaundice clearly has a distinct biochemical mechanism, and this factor cannot be explained on the basis of the morphologic criteria. I suspect that these biochemical and toxic factors may account for some of the cases you referred to in which you did not find exact correlation between the morphologic involvement and the degree of jaundice.

**EUGENE C. BEATTY, JR.:** The answer to Dr. Sunderland's question on the problem of ascites and peripheral edema is complicated by the fact that the illness of the patient is terminal, usually with low serum proteins. However, in these cases there was a high degree of correlation of the ascites at death.

Dr. Angrist's two questions; first of all, the problem of bile casts. It has been suggested that they may be correlated with the degree of jaundice in the patient, and in our cases generally the jaundice was of low grade, most of them running under 10, using bilirubin as the criterion for the degree of jaundice, and perhaps for that reason, the mildness of the jaundice in many cases would preclude the formation of bile thrombi in the terminal canaliculi. As for the rapidly developing anemia in some of these cases, perhaps these would fall into the group of secondary hypersplenism with increased erythrocyte fragility.

In answer to Dr. Sproul's question, the hepatotoxic drug I was referring to chiefly was nitrogen mustard, and the evidence for that is somewhat equivocal. However, I believe that Dameshek and some other workers gave nitrogen mustards to experimental animals and also studied autopsy material at various times after the drug had been given, and were able to observe that they did attack the liver by producing a polymorphonuclear infiltrate in the parenchyma shortly after the drugs were given, and then produced subsequent necrosis of liver tissue which was apparently maximal at about nineteen days. Then his material, in time, jumped a long span, so that after fifty-eight days had elapsed he was able to determine that the liver had pretty well regenerated and he suggested that perhaps the nitrogen mustard given to a patient with a relatively intact liver would not produce any serious damage, but perhaps in the overburdened liver, the nitrogen mustard added enough damage to the liver with the subsequent manifestation of jaundice in the patient.

As for the reticulum stain, we did not do reticulum or trichrome stains, Dr. Morrione, so I cannot answer your question about the correlation.